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Neuropsychological Effects of Caffeine: Is Caffeine Addictive?

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Abstract

Caffeine is the most widely used psychotropic drug in the world. Most of the caffeine consumed comes from coffee bean (i.e., a misnomer for the seed of *Coffea* plants), beverages (i.e., coffee, tea, soft drinks), in products containing cocoa or chocolate and in medications (i.e., analgesics, stimulants, weight-loss products, sports nutrition). The most prominent behavioral effects of caffeine take place over low to moderate doses are amplified alertness and attention. Moderate caffeine consumption leads very rarely to health risks. Higher doses of caffeine encourage negative effects such as anxiety, insomnia, restlessness and tachycardia. The habitual use of caffeine causes physical dependence that displays as caffeine withdrawal symptoms that harm normal functioning. Contrariwise, rarely high doses of caffeine can encourage psychotic and manic symptoms usually, sleep disturbances and anxiety. Even though caffeine does not engender life-threatening health difficulties frequently related to the utilization of drugs of addiction, for example amphetamine, cocaine and heroin, an incrementing number of clinical studies are exhibiting that some caffeine users become dependent on the drug and are unable to reduce consumption despite knowledge of recurrent health complications linked to constant use. The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), includes caffeine addiction and withdrawal as mental disorders. The World Health Organization (WHO) identifies caffeine dependence as a clinical disorder. Furthermore, diagnosis process of caffeine dependence syndrome is accepted by International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). Therefore the intention of this study was to analyze the neuropsychological effects of caffeine and try to assess in which respect caffeine could be considered a potential drug of addiction.

Keywords: Caffeine; Neuropsychological effect; Alertness; Addiction; Dependence; Drugs of addiction

Abbreviations: CNS: Central nervous system; BCE: Before common era; WHO: World Health Organization; FDA: Food and Drug Administration; GRAS: Generally recognized as safe; LD_{50}: Lethal dose, 50%; Aβ: Aamyloid-β; PD: Parkinson's disease; AD: Alzheimer's disease; CYP: Cytochrome; REM: Rapid eye movement; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition; APA: American Psychiatric Association; ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th revision; OTC: Over-the-counter; CGI: Clinical Global Impression; SCID: Structured Clinical Interview for DSM-IV; t.i.d: Thrice a day; b.i.d: Twice a day.

Introduction

Caffeine is one of the world's most consumed psychoactive substances and central nervous system (CNS) stimulant [1]. Unlike many other psychoactive substances, it is legal and unregulated in nearly all parts of the world [2]. As indicated by Chinese legend, the Chinese sovereign Shennong, presumed to have reigned in around 3000 BCE, coincidentally discovered tea when he noticed that when certain leaves fell into boiling water, a fragrant and revitalizing drink came about [3]. In 1819, for the first time, the German scientist Friedlieb Ferdinand Runge isolated, relatively unadulterated caffeine, he called it "Kaffebase" (i.e., a base that exists in coffee) [4]. On the other hand, in 1827, M. Oudry isolated "theine" from tea [5], however it was later confirmed by Mulder [6] and via Carl Jobst [7] that theine was actually caffeine. Hermann Emil Fischer was the first German chemist who synthesized caffeine from its chemical components and determined its structural formula in 1985 and 1987 successively [8]. In recognition of his work Fischer was awarded the Nobel Prize in 1902 [9]. Caffeine is a xanthine alkaloid occurring naturally in about 60 plant species, of which cocoa beans, kola nuts, tea leaves and coffee beans are the most understood. Other natural sources of caffeine include yerba mate, guarana berries, guayusa and the yaupon holly [10]. Caffeine is occasionally called guaranine when found in guarana, mateine when found in mate and theine when found in tea [11].

Caffeine is a CNS and metabolic stimulant and is utilized both recreationally and medically to diminish physical exhaustion and reestablish mental alertness when unusual weakness or drowsiness happens [12]. Caffeine fortifies the focal sensory system first at the higher levels, bringing about expanded sharpness and attentiveness, quicker and clearer stream of thought, expanded concentration and better body coordination and later at the spinal cord level at higher doses [13]. Once inside the body, it has mind boggling chemistry. It can treat and avert a range of conditions including broncho-pulmonary dysplasia and apnea of prematurity. It might give a humble defensive impact against few diseases [14], including Parkinson's disease (PD) [15] and certain types of cancer. One meta-analysis inferred that cardiovascular ailment for example, coronary artery disease and stroke are more improbable with 3 to 5 cups of non-decaffeinated coffee every day except more probable with more than 5 cups for every day [16]. Interestingly, caffeine citrate

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can be found in the model list of essential medicines of the World Health Organization (WHO) [17]. Few people encounter insomnia or sleep disruption if they intake caffeine, particularly amid the evening hours, yet others demonstrate little disturbance. Proof of hazard during pregnancy is obscure, a few authorities prescribe that pregnant ladies confine consumption to the equivalent of two cups of coffee per day or less [18,19]. Caffeine can evoke a mild type of drug dependence, connected with withdrawal symptoms such as sleepiness, headache, irritability and so on when an individual quits utilizing caffeine after rehashed everyday consumption [20,21]. Tolerance to the autonomic impacts of increased blood pressure and heart rate and increased urine output, creates with chronic use [22].

Food and Drug Administration (FDA) has categorized caffeine as "generally recognized as safe" (GRAS) [23]. Caffeine is infrequently considered as a dangerous substance. Physicians don't frequently attain information from patients about its utilization and investigation into caffeine utilization is not normally incorporated into psychiatric assessment [24]. Worldwide utilization of caffeine has been evaluated at 120,000 tons for every year, making it the world's most famous psychoactive substance [25]. In the Unified States, 87% of youngsters and adults routinely ingest caffeine, with adult caffeine consumers ingesting roughly 280 mg per day on average [26,27]. Administration of 1 to 1.5 g for each day is connected with a condition known as caffeinism [28]. Caffeinism ordinarily combines caffeine dependency with an extensive variety of obnoxious symptoms, including nervousness, irritability, restlessness, insomnia, headaches and palpitations after caffeine consumption [29]. Caffeine overdose can bring about a condition of CNS over-stimulation called caffeine intoxication [30]. This condition commonly happens, simply after ingestion of a lot of caffeine, well over the quantities found in common caffeinated beverages and caffeine tablets (e.g. more than 400 to 500 mg at once). The symptoms of caffeine intoxication are practically identical to the symptoms of overdoses of other stimulants for example, restlessness, fidgeting, anxiety, excitement, insomnia, increased urination, gastrointestinal disturbance, muscle twitching, a rambling flow of thought and speech, irritability, irregular or rapid heartbeat and psychomotor agitation [31]. In instances of much larger overdoses, mania, depression, lapses in judgment, disorientation, delusions, hallucinations, or psychosis may occur and rhabdomyolysis can be incited [32]. Massive overdose can even bring death [33]. The LD_{50} (lethal dose, 50%) of caffeine in people is reliant on individual sensitivity, but is assessed to be 150 to 200 mg for every kg of body mass (i.e., 75 to 100 cups of coffee for a 70 kg adult) [34]. Various fatalities have been brought about by overdoses of readily available powdered caffeine supplements, for which the evaluated lethal amount is not exactly a tablespoon [35]. The lethal dose is lower in people whose capacity to metabolize caffeine is weakened because of hereditary factors or chronic liver disease [36].

Caffeine is available in different consumer products that are the reason it is hard to attain at standard dose [37]. Normally, a cup of brewed coffee contains roughly 100 mg of caffeine, contrasted with 80 mg for instant coffee and 30 mg for instant tea [38], a can of coca-cola contains 34 mg [39]. Caffeine is added to numerous well known soft drinks and is additionally a part of various pharmaceutical products including analgesics, cold and flu medications, diet medications and diuretics [40,41]. Therefore the purpose of this study was to explore the neuropsychological effects of caffeine and its potentiality as a drug of addiction.

Pharmacological and physiological effects of caffeine

Caffeine is quickly and entirely absorbed from the gastrointestinal tract, with 99% being absorbed within 45 min of ingestion [42]. Peak plasma concentrations take place between 15 and 120 min after oral ingestion. This wide variation in time might be because of variation in gastric emptying time and the presence of other dietary constituents, for example, fiber [43]. Once the caffeine is absorbed there appears to be no hepatic first-pass impact [44]. It is eliminated by first-order kinetics and is satisfactorily portrayed by a one-compartment open model system [45]. Caffeine has a physiological half-life of 3.5 to 6 h [46,47]. Its physiological impacts are seen in less than 1 h [46]. Infants do not metabolize caffeine and therefore have a half-life of around 4 days [48].

The liver is the prime place for caffeine metabolism. Rate of metabolism varies across the population; the half-life is diminished in smokers, but augmented during pregnancy and in women taking oral contraceptives [49]. Cytochrome (CYP) P450 oxidase enzyme system is predominantly involved in caffeine metabolism. This metabolic process involves conversion of caffeine by the CYP1A2 isozyme into three dimethylxanthines [50], for example, paraxanthine (72%), theobromine (20%) and theophylline (8%) [51] each of which has its own effects for the body:

- Paraxanthine: Increases lipolysis, prompting to raise glycerol and free fatty acid levels in blood plasma [51].
- Theobromine: Dilates blood vessels and increases urine volume. Theobromine is additionally the key alkaloid in the cocoa bean [51].
- Theophylline: Relaxes smooth muscles of the bronchi and are utilized to treat asthma. The therapeutic dose of theophylline, however, is many times greater than the levels achieved from caffeine metabolism [51].

Further metabolism takes place in each of these metabolites, followed by renal excretion. Caffeine can accrue in people with severe liver disease as expressed before, expanding its half-life [52].

Caffeine plays role as an adenosine receptor antagonist, thus blocking endogenous adenosine to bind to the adenosine receptors. Along these lines, caffeine briefly counteracts drowsiness and consequently keeps up or reestablishes alertness [53]. Vitally, caffeine has been appeared to stimulate dopaminergic action by evacuating the negative modulatory impacts of adenosine at dopamine receptors. Studies recommend that dopamine discharge in the nucleus accumbens shell might be a particular neuropharmacological mechanism fundamental to the addictive capability of caffeine [54]. Up-regulation of the adenosine system after chronic caffeine consumption seems, apparently to be a neurochemical phenomenon underlying caffeine withdrawal disorder [55]. This mechanism results in increased functional sensitivity to adenosine during caffeine resistant and it likely plays a vital part in the behavioral and physiological impacts created by caffeine withdrawal.

The effects of caffeine in various organ systems are given below:

Effects of caffeine on the central nervous system

The most obvious effect of caffeine is alertness. At the larger amounts, it stimulates the CNS, the cortex subsequently medulla and just later stimulates the spinal cord. Its effects instigate within 1 h and keep going for 3 to 4 h [56,57]. In fact slight incitement of cortex is gainful for clear and critical thinking. Numerous findings recommended caffeine ingestion is connected with enhanced attention and fortified night driving [57]. The onset of the caffeine shows up within 1 h and goes on for 3 to 4 h [58]. Studies suggested that caffeine is linked to lower risk of several neurodegenerative diseases such as Alzheimer's disease (AD) and PD is given in Table 1.

Adenosine Receptor Antagonist	Alzheimer's Disease	Parkinson's Disease
Caffeine	Prevents the accretion of amyloid-β-peptide (Aβ) in and nearby cerebral blood vessels [59].	Increases motor activity [60].
	Reverses cognitive dysfunction and reduces brain Aβ levels in AD mice [61].	Down-regulates neuroinflammatory responses and nitric oxide formation [62]
	Intake of 3 to 5 cups coffee per day at midlife is linked with a diminished risk of dementia or AD by about 65% in later life [63].	Reduces both motor and non-motor early onset symptoms [64].
	Protects contrary to oxidative stress and AD-like pathology in rabbit hippocampus [65].	Inhibits the loss of nigral dopaminergic neurons [66].
	Increases mitochondrial function and blocks melatonin signaling to mitochondria [67].	Protects in contrast to disturbances of the blood-brain barrier in animal models [68].

Table 1: Effects of caffeine on neurodegenerative disorders [59-68].

Around 150 to 250 mg of caffeine (i.e., 1 to 2 cups of coffee) is sufficient to incite adverse impacts. Nonetheless, the relationship amongst caffeine and cerebral pains is confounded [69]. An excessive amount of caffeine can bring about headache. However, suddenly stopping ordinary consumption of caffeine can likewise bring about headache. Caffeine is used in some over-the-counter (OTC) and prescription-strength migraine and headache medications [69]. Vast amounts of caffeine may bring about hyperesthesia, an unpleasant sensory sensation and so forth. It is likewise conceivable to overdose on caffeine. Confusion and hallucinations are basic manifestations of a caffeine overdose. Furthermore, an overdose can even bring about death because of convulsions [69].

Effects of caffeine on the digestive and excretory systems

Several studies have recommended that caffeine consumption can increase the gastric juice secretion which may even cause acid reflux or upset stomach even ulcer [70]. Emesis can be triggered by coffee moreover; it can induce catecholamine release from the adrenal medulla. It can also act as a potent diuretic and also can potentiate blood flow, glomerular filtration rate and rennin discharge [69].

Effects of caffeine on the cardiovascular and respiratory systems

Similar to CNS, the impact of caffeine in the cardiovascular system is less significant. Essentially its direct stimulatory impact on the heart might be counterbalanced by its central vagus incitement. Just at high doses the direct effect dominates [71,72]. However, in limited doses, caffeine can increase the conductibility of the heart and changes the electro-physiological action. Heavy caffeine intake increases the plasma levels of homocystine, which is a risk factor for coronary illness. Caffeine is a vasoconstrictor, it increases plasma epinephrine and norepinephrine levels in non-habitual users that may small rise in blood pressure that generally comes back to pre-ingestion level after 3 to 4 h. Caffeine actuates different intense cardiovascular impacts, for example, an up regulation of circulating catecholamines [71,72]. Arterial stiffness and endothelium dependent vasodilatation also may take place, prompting to increments in systolic and diastolic blood pressure [73]. Caffeine empowers respiration and this impact is refereed by the two fundamental neurotransmitters for example, dopamine and seratonin. Theophylline, which is a tracheal smooth muscle relaxant, is effective to control asthma [72]. An expansion in the respiration rate is the prime impact reliant on the plasma caffeine level [74]. The therapeutic effect is seen at a plasma concentration of over 10 mg/L, however 20 mg/L is connected with adverse effects. However, caffeine overdose may cause rapid or irregular heartbeat and breathing suffering. In some cases, caffeine overdose can bring about death due to convulsions or irregular heartbeat [72].

Positive Effect	Negative Effect
Alertness	Anxiety
Attention	Depression
Concentration	Irritable
Focus	Addiction

Table 2: Positive and negative psychological impacts of caffeine [85].

Effects of caffeine on the skeletal and muscular systems

Caffeine influences skeletal muscle contractility. In large quantities, caffeine may meddle with absorption and calcium metabolism, which may potentiate osteoporosis [69,72,75]. Caffeine can trigger mobilization of calcium from cells and may hasten bone loss. Symptoms of caffeine withdrawal incorporate achy muscles. Tremor is a common side effect of caffeine ingestion. An overdose may also lead to muscle twitches [69,72,75].

Effects of caffeine on the reproductive system

Caffeine, especially in doses of 300 mg (i.e., 3 cups of coffee) or more every day, can causes male and female infertility. Some studies recommend that a lot of caffeine can meddle with estrogen production and metabolism, making it tougher to get pregnant [69,72,75]. Caffeine can cross into the placenta barrier. Being a stimulant, it can upsurge the heart rate and metabolism of the baby. Consumption of a lot of caffeine can potentiate the danger of miscarriage and also can bring about congenital deformities, fetal growth retardation and residual effects in the newborn [69,72,76].

Psychological effects of caffeine

Caffeine can bring about various measures of psychological effects (Table 2) relying on the individual and the concentration. Low doses of caffeine cause augmented alertness and diminished weariness [77]. In moderate doses, caffeine may lessen symptoms of depression and lower suicide chance [78] while high dosages can bring about the repulsive impacts of caffeinism [79]. One or two cups of coffee (i.e., 150 to 250 mg of caffeine) can have truly unfavorable impacts on one's mental state. A consumption of only 100 mg of caffeine can prompt such symptoms as dizziness, anxiety, irritability, restlessness, sleep deprivation and headaches in few people. The individuals who frequently ingest caffeine, whether in pills, food or beverage, would be less vulnerable to these impacts at a low concentration yet have different issues to confront [72,80].

Caffeine is a drug and with repetitive administration it allows the body to develop dependence. This can happen within 6 to 15 days of administration [80,81]. In the event that caffeine is not devoured routinely after this period one may feel lethargic until the drug is ingested. People dependent on caffeine start to show symptoms of withdrawal after admission is halted for the period of 12 to 24 h [80,81].

Contingent upon the individual, the standard symptoms of withdrawal incorporate headache, weariness, lack of care and even anxiety. These symptoms crest around 36 h and proceed for up to 1 week after caffeine deficiency. The body's system of withdrawal can be decreased through dose adjustments or through analgesic drugs [80,81].

Large dosages of caffeine can originate another sort of disorder known as caffeinism. In human, ingestion of 650 mg of caffeine for every day can prompt this syndrome [80,82]. This sum can prompt to aggressiveness and psychotic behavior. This syndrome is indistinct from the mental disorder like anxiety neurosis making the individual seem confused or confounded with true psychotic states [80,82]. Albeit much caffeine must be ingested for caffeinism to set in, sleep is exceptionally defenseless against even the smallest caffeine consumption [80,82]. Sleep can be incredibly influenced by ingestion of caffeine before bed. Much of the time caffeine causes people to set aside a more extended opportunity to fall asleep, diminishing the total amount of sleep received. This influence, poor sleepers more radically than heavy sleepers. Caffeine has likewise been resolved to influence the phases of sleep and sometimes influences the rapid eye development (REM) phase of sleep [75,80,83].

Children are significantly more vulnerable to caffeine consumption symptoms and should drastically limit their intake. Caffeine ought to be evaded or utilized mindfully with medications like dextramphetamine, methylphenidaten, nicotine, pemoline, psuedoephedrine, phenylpropanolamine and sympathomimetics. Merging these medications with caffeine can bring about anxiety, tetchiness and insomnia [80,84].

Caffeine-induced psychiatric disorders

The role of consumption of caffeine in psychiatric disorders is unavoidable. Caffeine use has been connected with numerous disorders such as anxiety, sleep and eating disorders and there is a possible association with schizophrenia.

Anxiety disorders

Several studies suggested that caffeine is associated with anxiety disorders [86,87]. The increased levels of lactate in the brain are considered as a possible reason against caffeine-induced anxiety [88,89]. In addition, the function of adenosine in interceding caffeine-induced anxiety is claimed by the several findings [90]. In case of people with panic disorder and social phobia, intake of caffeine can increase the sensitivity [91].

Sleep disorders

It is well-recognized that caffeine causes insomnia. It decreases slow-wave sleep as well as can lessen REM sleep in the early part and later of the sleep cycle respectively [92]. Caffeine intake instantly preceding to bedtime or all over the day has been revealed to delay the onset of sleep, reduce total sleep time and modifies the regular stages of sleep. Actually, caffeine-mediated sleep disruption is extreme amid individuals who are not regular caffeine users [93]. Even though there is proof for some tolerance to the sleep disturbing action of caffeine, full tolerance may not happen and consequently, habitual caffeine consumers are susceptible to caffeine-mediated sleep difficulties [93].

Eating disorders

The study proposed that caffeine is associated with eating disorders for example, people with bulimia and anorexia nervosa frequently intake large amounts of caffeine containing products mainly drinks, in the trust that caffeine raises the metabolic rate as well as suppresses appetite [94,95]. Astonishingly, caffeine-induced eating disorders have received little attention owing to lack of findings. In case of patients with anorexia nervosa incidence of high risk of cardiac arrhythmias, the stimulating consequence of caffeine on the heart may be hazardous. In addition administration of excessive caffeine may also accountable for osteoporosis for patients with a high prevalence in anorexia nervosa [94,95].

Schizophrenia

Studies suggested that patients with schizophrenia have higher than typical intakes of caffeine, but the results are inconsistent [96]. This high intake is moderately linked to the extreme cigarette smoking frequently saw in these patients [97]. However, this may due to counterpoise the sedating effects of antipsychotic medication. Lots of psychotropic drugs also cause dry mouth, which might upsurge the consumption of caffeinated drinks. In addition, high caffeine intake is associated with delusions and hallucinations by people both with [96,98] and without psychosis [99].

DSM-IV Criteria for Caffeine-Induced Psychiatric Disorders
Caffeine Intoxication
• Demonstration of 5 or more of the following signs during or shortly after caffeine use: Restlessness Nervousness Excitement Insomnia Flushed face Diuresis Gastrointestinal disturbance Muscle twitching Rambling flow of thought and speech Tachycardia Periods of inexhaustibility Psychomotor agitation • The aforementioned symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. • The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder, such as an anxiety disorder.
Caffeine-Induced Anxiety Disorder
• Prominent anxiety predominates in the clinical picture. • There is evidence from the history, physical examination or laboratory findings suggesting that the anxiety developed within 1 month of caffeine intoxication or withdrawal or that medications containing caffeine are etiologically related to the disturbance. • The disturbance is not better accounted for by an anxiety disorder that is not substance-induced. • The disturbance does not occur exclusively during the course of a delirium. • The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Caffeine-Induced Sleep Disorder
• A prominent disturbance in sleep occurs that is sufficiently severe to warrant independent clinical attention. • There is evidence from the history, physical examination, or laboratory findings that the sleep disturbance is the direct physiological consequence of caffeine consumption. • The disturbance is not better accounted for by another mental disorder. • The disturbance does not occur exclusively during the course of a delirium. • The disturbance does not meet the criteria for breathing-related sleep disorder or narcolepsy. • The sleep disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Caffeine-Related Disorder Not Otherwise Specified
• This includes any caffeine disorder other than those previously listed. • Symptoms of caffeine withdrawal that are not currently an officially recognized diagnosis are present.

Table 3: DSM-IV criteria for caffeine intoxication, caffeine-induced anxiety disorder, caffeine-induced sleep disorder and caffeine-related disorder not otherwise specified [100].

There are four caffeine-mediated psychiatric disorders documented by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), manual of the American Psychiatric Association (APA) these are caffeine intoxication, caffeine-induced anxiety disorder, caffeine-induced sleep disorder and caffeine-related disorder not otherwise specified are mentioned in Table 3 [100].

Caffeine addiction and dependence

Structurally caffeine and adenosine is very close presented in Figure 1 [101]. Furthermore, caffeine can function in a similar manner in the brain and it can also block adenosine receptors in the brain cells. The stimulant effect of caffeine is largely due to this blocking of adenosine receptors [102]. Because without this antagonistic effect, adenosine will be able to bind with the adenosine receptors and will trigger cellular response eventually lead to increased drowsiness. As a result, caffeine temporarily prevents or relieves drowsiness and thus maintains or restores alertness [103].

Regular intake of caffeine can affect the chemistry and activity of the brain. The primary reason behind this is, as adenosine receptors are being antagonized by caffeine on a regular basis, the human body generates additional adenosine receptors to manage the change. Henceforth, the additionally generated receptors may require more caffeine. Thus, all of a sudden when the caffeine supply is ceased, withdrawal symptoms like tiredness and irritability is noticed as the body has the additional adenosine receptors which are not blocked [104,105]. As indicated by researchers, the previously mentioned lack of antagonism is not the only problem. The findings of some studies also indicate that level of dopamine also slightly increases due to the consumption of caffeine, which ultimately can lead to a mild version of euphoria as experienced by powerfully addictive drug like cocaine users [106]. Regular use of caffeine is responsible for mild physical dependence. But caffeine does not threaten the physical, social or economic health and caffeine addiction is not like drug addiction [107]. Another reason to repeated consumption of coffee is its induced positive feelings [108].

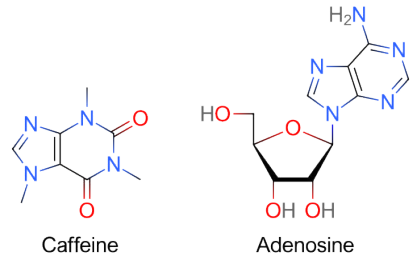

Figure 1: Structure of caffeine and adenosine.

However, experts have disagreed with regard to whether caffeine is truly an addictive substance. Actually, caffeine withdrawal is comparatively short-lived and rarely serious with respect to that of addictive prescription drugs or street drugs [109]. In fact, reliable sources are suggested that caffeine is not truly addictive [109]. Now caffeine meets the norms for being an addictive substance in terms of dependence, tolerance and withdrawal [110]. At present the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), the APA standard guide of mental disorders, comprises caffeine addiction and caffeine withdrawal as familiar mental disorders [111]. DSM-5 diagnostic criteria for caffeine use disorder are offered in Table 4. In addition, several studies have resolved that several caffeine users become genuinely addicted (Table 5) [78].

The WHO identifies the addiction of caffeine as a real disorder [111,112]. The diagnostic process of caffeine dependence syndrome is recognized by International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) developed by WHO [121,122]. This disorder comprises a collection of behavioral, cognitive and physiological phenomena which actually develop following recurrent use of the substance (i.e., caffeine). Furthermore, this disorder also involves strong urge to take that substance, uncontrolled use, continuing the use of the drug even after the detrimental consequences, increased tolerance, occasionally a physical withdrawal state and setting priority over other activities and responsibilities to take that substance [121].

Caffeine withdrawal

A lot of rigorous double-blind studies showed the caffeine withdrawal syndrome. The possibility of caffeine withdrawal that may result in clinically significant distress or impairment in functioning is revealed by the state of including caffeine withdrawal as an official diagnosis in the ICD-10, DSM-IV and DSM-5 [121-123]. Although most research provides an idea of withdrawal that has been conducted by adults, but there are also some evidences that children experience withdrawal effects during caffeine abstinence [121-123].

There are many symptoms experiencing while withdrawing caffeine. Not everyone is going to experience all of these symptoms. Some may feel headache and sluggish. Some others may have a variety of symptoms that may make life difficult to deal with for a couple of weeks [124]. The most commonly reported withdrawal symptoms are

DSM-5 Caffeine Use Disorder Diagnosis Scheme
A problematic pattern of caffeine use leading to clinically significant impairment or distress, as manifested by at least the first three of the following criteria occurring within a 12 month period: • A persistent desire or unsuccessful efforts to cut down or control caffeine use. • Continued caffeine use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by caffeine. • Withdrawal, as manifested by either of the following: The characteristic withdrawal syndrome for caffeine. Caffeine (or a closely related substance) is taken to relieve or avoid withdrawal symptoms. • Caffeine is often taken in larger amounts or over a longer period than was intended. • Recurrent caffeine use resulting in a failure to fulfill major role obligations at work, school or home (e.g. repeated tardiness or absences from work or school related to caffeine use or withdrawal). • Continued caffeine use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of caffeine (e.g. arguments with spouse about consequences of use, medical problems, cost). • Tolerance, as defined by either of the following: A need for markedly increased amounts of caffeine to achieve the desired effect. Markedly diminished effect with continued use of the same amount of caffeine. • A great deal of time is spent in activities necessary to obtain caffeine, use caffeine or recover from its effects. • Craving or a strong desire or urge to use caffeine.

Table 4: DSM-5 diagnostic criteria for caffeine use disorder [112].

Name of the Study	Study Design	Result (%)									
		Persistent Desire or Unsuccessful Efforts to Cut Down Use	Use Despite Harm	Withdrawal	Endorsed All Three Primary Criteria	Use More than Intended	Use Results in Dysfunction	Use Despite Interpersonal Problems	Great Deal of Time Spent With Drug	Tolerance	Craving
Hughes et al. [113]	Randomly-selected caffeine users were asked about generic DSM-IV criteria for dependence, abuse, intoxication and withdrawal pertaining to their caffeine use in the last year via a structured telephone interview.	56	14	18	9	28	15	2	50	8	19
Ciapparelli et al. [114]	Healthy subjects were assessed by the Structured Clinical Interview for DSM-IV (SCID) and by a structured interview for caffeine intoxication and withdrawal and for substance dependence applied to caffeine use. Out- and in-patients, suffering from different psychiatric disorders, were also involved in the study.	20	24	2	–	50	–	–	13	11	–
Striley et al. [115]	High school and college students, drug treatment patients and pain clinic patients who reported caffeine use in the last 7 days and also reported use of alcohol, nicotine, or illicit drugs within the past year were assessed about caffeine use and dependence symptoms.	23	44	26	20	17	–	–	40	13	34
Juliano et al. [116]	Subjects who identified as being psychologically or physically dependent on caffeine, or who had tried unsuccessfully to modify caffeine consumption participated in a face-to-face diagnostic clinical interview. They also completed measures concerning caffeine use and quitting history, reasons for seeking treatment and standardized self-report measures of psychological functioning.	89	87	96	79	38	–	–	61	70	86
Svikis et al. [117]	Women seeking obstetrical care in an office-based practice completed questionnaires and provided saliva samples at three prenatal visits occurring 2-3, 3-4, and 7 months post-conception. On visit 1, the patients received the physician's instructions to stop using caffeine. Structured interviews were used to assign a diagnosis of caffeine dependence (lifetime) and to identify family history of alcoholism. Outcome measures included self-reported levels of caffeine use and saliva caffeine levels at the three prenatal visits.	45	43	77	–	45	–	–	25	50	27
Jones and Lejuez [118]	University students were evaluated about personality correlates of caffeine consumption and dependence in 60 university students. Self-report and behavioral measures of sensation seeking, impulsivity and risk taking were administered to 2 groups, identified as caffeine dependent-high consuming or caffeine nondependent-low consuming.	60	57	73	–	83	–	–	77	70	–
Strain et al. [119]	Subjects who reported problems with their use of caffeine for evidence suggesting a diagnosis of caffeine dependence were assessed for caffeine dependence based on the generic DSM-IV.	61	94	94	–	–	–	–	–	75	–
Bernstein et al. [120]	Adolescents who consumed caffeine daily and had some features of caffeine dependence on telephone screens were scheduled for outpatient evaluation. The evaluation included the Diagnostic Interview Schedule for Children-IV-Youth Version (DISC-IV) and modified DISC-IV questions that assessed caffeine dependence based on DSM-IV substance dependence criteria.	39	17	78	22	–	–	–	–	42	–

Table 5: Prospective epidemiologic studies for caffeine use disorder and the prevalence of the disorder based on DSM-IV criteria [113-120].

DSM-5 Diagnostic Scheme for Caffeine Withdrawal
• Prolonged daily use of caffeine. • Abrupt cessation of or reduction in caffeine use, followed within 24 h by three (or more) of the following signs or symptoms: Headache Marked fatigue or drowsiness. Dysphoric mood, depressed mood, or irritability. Difficulty concentrating. Flu-like symptoms (nausea, vomiting, or muscle pain/stiffness). • The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. • The signs or symptoms are not associated with the physiological effects of another medical condition (e.g. migraine, viral illness) and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

Table 6: DSM-5 diagnostic criteria for caffeine withdrawal conditions [112].

headache, fatigue, drowsiness, dysphoric mood, irritability, depression, nausea, muscle aches and impairment of cognitive or behavioral performances [125,126]. In Table 6, the DSM-5 diagnostic measures for caffeine withdrawal situations are expressed [112].

Severity of caffeine withdrawal is an increasing function of daily self-reported caffeine dose. Caffeine withdrawal has been shown to occur after abstinence from a dose as low as 100 mg per day. It is seen that caffeine withdrawal has been shown to occur after stopping regular once-a-day consumption of caffeine [127].

Normal caffeine consumers who abstain for 24 h indicate that the incidence of withdrawal headache is about 50%. When all withdrawal symptoms are considered, the incidence of caffeine withdrawal is higher. A population based random survey suggests that, 40 to 70% of individuals who tried to quit caffeine use reported experiencing withdrawal symptoms. Many caffeine consumers may be unaware of their physical dependence on caffeine because their frequent habitual consumption precludes a period of sustained abstinence. Also, it is seen that relatively low doses of caffeine can partially suppress withdrawal symptoms. People may report never experiencing withdrawal because they unknowingly consumed small amounts of caffeine on days they thought they had been caffeine free. Moreover, caffeine withdrawal symptoms such as headache, nausea, muscle aches, etc. may be misattributed to other causes like viral infection [127,128].

Caffeine withdrawal has been documented to produce clinically significant distress in daily functioning. It is seen that in a caffeine-withdrawal evaluation experiment, 73% of individuals who met criteria for DSM-IV substance dependence on caffeine reported functional impairment in normal activities during an experimental withdrawal phase. The proportion of regular caffeine consumers who are at risk for experiencing such functional impairment during caffeine withdrawal is difficult to estimate. One experimental study with individuals from the general community has showed that, 52% of individuals from the general community with an average caffeine intake of 260 mg per day reported moderate to severe headache and 8 to 11% showed abnormally high scores on standardized depression, anxiety and fatigue scales [21,127]. Another study has shown that, 45% of individuals experienced a diffuse, throbbing headache, reporting syndromes like nausea and sickness [21,127].

Not same type of symptoms and severity has been found on the caffeine withdrawal, but there are considerable differences within and across the individuals. Only half of the regular caffeine consumers were found to have headache after the single episode of caffeine withdrawal [127,129]. Variation within and across subject was clearly observed from a study that monitored the repeated abstinence trials. It was found that no headache was reported in one of the subject, continuous headaches in some others while headaches were reported on some subjects in some of the trial but not for other trials. However, there has been little information on the determinants of these differences within and across individuals [127,129].

The syndrome of caffeine withdrawal occurs in an orderly fashion. The symptoms begin 12 to 24 h after abstinence from caffeine intake. However, onset of symptom as late as 36 h has also been observed. The peak intensity of symptoms has been found to occur 20 to 48 h after the withdrawal. The withdrawal symptoms occur, usually for a period of 2 days to 1 week. However, symptoms have been reported for even longer periods for some subjects [124,127].

Caffeine tolerance

Tolerance can be defined as a decrease in the response to a drug after the repeated exposure to that drug. Administration of high doses of caffeine (i.e., 750 to 1200 mg per day spread throughout the day), have been shown to produce complete tolerance to some, but not all the effects of caffeine [130]. However, the administration of lower or typical dietary doses of caffeine produces incomplete tolerance. For example, the subject who consumes caffeine regularly may experience disturbance in sleep. The extent of caffeine tolerance may depend on several factors like amount, dose and frequency of administration. It may also depend on individual variation found in the elimination of the caffeine [130].

When high doses of caffeine (e.g. 300 mg t.i.d for 18 days) were administered, complete tolerance was developed in control human laboratory studies [131]. However, lower doses (i.e., 200 mg b.i.d for 7 days) did not demonstrate complete tolerance [131]. Similarly, complete tolerance to blood pressure and other physiological effects (i.e., plasma non-epinephrine and epinephrine and plasma rennin activity) have been observed in the administration of high dose of caffeine (e.g. 250 mg t.i.d for 4 days), but only partial tolerance to blood pressure and middle cerebral artery velocity have been observed at slightly lower doses (i.e., 200 mg b.i.d for 7 days) [131,132]. Substantial but in complete tolerance has been shown to the sleep disruptive effects of high dose of caffeine (e.g. 400 mg t.i.d for 7 days) [132].

Reinforcing effects of caffeine

The reinforcing efficacy of a drug defined as the corresponding efficacy in establishing or maintaining a behavior so that the delivery of the drug is not independent [133]. Caffeine shows a widely recognized behavioral stimulant and mildly reinforcing properties which are probably responsible for the maintenance of caffeine self-administration, primarily in the form of caffeinated beverages, such as coffee, tea and cola [134]. Controlled double-blind laboratory studies show that subjects will choose caffeine over placebo in double-blind choice procedures, as well as perform work or forfeit money in exchange of caffeine. When multiple self-administration opportunities are available within a day, doses as low as 25 mg [20] are reinforcing [135,136]. When self-administration is limited to once a day, when doses of 100 and 200 mg are reinforcing, while doses of 400 mg and greater tend to be avoided [137]. Recent research shows that caffeine reinforcement occurs in 100% of heavy caffeine consumers that also had histories of drug abuse [138,139]. For moderate caffeine users, caffeine reinforcement occurs in about 45% to 80–100% of the experimental subjects [135,140-142].

Caffeine reinforcement differs with the dose and the dosage of caffeine encountered in tea and coffee are high enough because they are the high reinforcer, since people look for them in case of withdrawal symptoms [143]. Actually, a dose of 25 to 50 mg caffeine containing a cup of coffee acts as a reinforcer, while increasing doses beyond 50 or 100 mg tends to decrease the choice of caffeine, or the frequency of caffeine self-administration [135] and high doses of caffeine (i.e., 400 to 600 mg in a single dose) are avoided [144]. There is a quite a bit of individual variability in the reinforcing effects of caffeine. Across studies, the overall incidence of caffeine reinforcement in normal caffeine users is approximately 40%, with a higher incidence (i.e., 80 to 100%) of reinforcement under conditions of repeated caffeine exposure [145]. In some studies, caffeine consumer tends to report positive subjective effects, whereas who choose placebo is more likely to report negative subjective effects (e.g. nervousness) at low to moderate doses [145].

The reinforcing effects of caffeine can be increased the effect or likelihood by the caffeine physical dependence. For example, caffeine consumers were more than twice as likely to show caffeine reinforcement if they reported caffeine withdrawal symptoms after drinking

decaffeinated coffee [128]. In case of studies in which caffeine physical dependence was experimentally manipulated, subjects are more than twice as likely to choose caffeine over placebo when they are physically dependent [146,147]. There is also evidence that avoidance of caffeine withdrawal determines caffeine consumptions to a greater extent than the positive effects of caffeine [147-149]. Caffeine reinforcement also gives the impression of being influenced by task requirements. For example, in a double-blind study, subjects chose caffeine over placebo when required to perform an attentiveness job, but chose placebo over caffeine when required to engage in relaxation [150].

Current studies have mentioned a flavor preference for example an indirect measure of caffeine reinforcement [151,152]. Subjects who are continually exposed to a novel flavored drink combined with caffeine improve the ratings of drink pleasantness, whereas subjects receiving placebo-paired drinks show decreased ratings of drinks pleasantness [153,154]. It seems plausible that flavor drink combined with caffeine plays an important role in the development of consumer preferences for different types of caffeine-containing beverages.

Caffeine contents in food, beverage and pharmaceutical products

Caffeine is the most widely consumed stimulant in the world as stated earlier, which is found in highest concentration in coffee as well as tea, cola drinks, chocolate candy and cocoa. Caffeine is considered as

Product	Serving Size	Caffeine Content (mg)
OTC Drugs		
Analgesics	2 tablets	64 or 130 mg
Stimulants	1 tablet	100 or 200 mg
Weight-loss products	2-3 tablets	80-200 mg
Sports nutrition	2 tablets	200 mg
Coffees		
Coffee, brewed	8 ounces	135
General Foods International Coffee, Orange Cappuccino	8 ounces	102
Coffee, instant	8 ounces	95
General Foods International Coffee, Cafe Vienna	8 ounces	90
Maxwell House Cappuccino, Mocha	8 ounces	60-65
General Foods International Coffee, Swiss Mocha	8 ounces	55
Maxwell House Cappuccino, French Vanilla or Irish Cream	8 ounces	45-50
Maxwell House Cappuccino, Amaretto	8 ounces	25-30
General Foods International Coffee, Viennese Chocolate Cafe	8 ounces	26
Maxwell House Cappuccino, decaffeinated	8 ounces	3-6
Coffee, decaffeinated	8 ounces	5
Tea		
Celestial Seasonings Iced Lemon Ginseng Tea	16 ounce bottle	100
Bigelow Raspberry Royale Tea	8 ounces	83
Tea, leaf or bag	8 ounces	50
Snapple Iced Tea, all varieties	16 ounce bottle	48
Lipton Natural Brew Iced Tea Mix, unsweetened	8 ounces	25-45
Lipton Tea	8 ounces	35-40
Lipton Iced Tea, assorted varieties	16 ounce bottle	18-40
Lipton Natural Brew Iced Tea Mix, sweetened	8 ounces	15-35
Nestea Pure Sweetened Iced Tea	16 ounce bottle	34
Tea, green	8 ounces	30
Arizona Iced Tea, assorted varieties	16 ounce bottle	15-30
Lipton Soothing Moments Blackberry	Tea 8 ounces	25
Nestea Pure Lemon Sweetened Iced Tea	16-ounce bottle	22
Tea, instant	8 ounces	15
Lipton Natural Brew Iced Tea Mix, diet	8 ounces	10-15
Lipton Natural Brew Iced Tea Mix, decaffeinated	8 ounces	<5
Celestial Seasonings Herbal Tea, all varieties	8 ounces	0
Celestial Seasonings Herbal Iced Tea, bottled	16-ounce bottle	0
Lipton Soothing Moments Peppermint Tea	8 ounces	0
Soft Drinks		
Mountain Dew	12 ounces	55
Surge	12 ounces	51
Diet Coke	12 ounces	47
Coca-Cola	12 ounces	45
Dr. Pepper, regular or diet	12 ounces	41
Sunkist Orange Soda	12 ounces	40
Pepsi-Cola	12 ounces	37
Barqs Root Beer	12 ounces	23
7-UP or Diet 7-UP	12 ounces	0
Barqs Diet Root Beer	12 ounces	0
Caffeine-free Coca-Cola or Diet Coke	12 ounces	0
Caffeine-free Pepsi or Diet Pepsi	12 ounces	0
Minute Maid Orange Soda	12 ounces	0
Mug Root Beer	12 ounces	0
Sprite or Diet Sprite	12 ounces	0
Caffeinated Waters		
Java Water	1/2 liter (16.9 ounces)	125
Krank 20	1/2 liter (16.9 ounces)	100
Aqua Blast	1/2 liter (16.9 ounces)	90
Water Joe	1/2 liter (16.9 ounces)	60-70
Aqua Java	1/2 liter (16.9 ounces)	50-60
Juices		
Juiced	10 ounces	60
Frozen Desserts		
Ben & Jerry's No Fat Coffee Fudge Frozen Yogurt	1 cup	85
Starbucks Coffee Ice Cream, assorted flavors	1 cup	40-60
Häagen-Dazs Coffee Ice Cream	1 cup	58
Häagen-Dazs Coffee Frozen Yogurt, fat-free	1 cup	40
Häagen-Dazs Coffee Fudge Ice Cream, low-fat	1 cup	30
Starbucks Frappuccino Bar	1 bar (2.5 ounces)	15
Healthy Choice Cappuccino Chocolate Chunk or Cappuccino Mocha Fudge Ice Cream	1 cup	8
Yogurts (single container)		
Dannon Coffee Yogurt	8 ounces	45
Yoplait Cafe Au Lait Yogurt	6 ounces	5
Dannon Light Cappuccino Yogurt	8 ounces	<1
Stonyfield Farm Cappuccino Yogurt	8 ounces	0
Chocolates or Candies		
Hershey's Special Dark Chocolate Bar	1 bar (1.5 ounces)	31
Perugina Milk Chocolate Bar with Cappuccino Filling	1/3 bar (1.2 ounces)	24
Hershey Bar (milk chocolate)	1 bar (1.5 ounces)	10
Coffee Nips (hard candy)	2 pieces	6
Cocoa or Hot Chocolate	8 ounces	5
Note: Serving sizes are based on commonly eaten portions, pharmaceutical instructions, or the amount of the leading-selling container size. For example, beverages sold in 16 ounce or half-liter bottles were counted as one serving.		

Table 7: The typical caffeine content of common foods, beverage and pharmaceutical products [157].

Energy and Soft Drinks	Caffeine Content (mg)
Higher Caffeine Energy Drinks	
Wired X505	505
Fixx	500
BooKoo Energy	360
Wired X344	344
SPIKE Shooter	300
Viso Energy Vigor	300
Cocaine Energy Drink	280
Jolt Cola	280
NOS	250
Redline RTD	250
Blow (Energy drink mix)	240
Lower Caffeine Energy Drinks	
Bomba Energy	75
HiBall Energy	75
Airforce Nutrisoda Energize	50
Whoop Ass	50
Vitamin Water (Energy citrus)	50
Top Selling Energy Drinks	
Red Bull	80
Monster	160
Rockstar	160
Full throttle	144
No Fear	174
Amp	75
SoBe Adrenaline Rush	79
Tab Energy	95
Classic Soft Drinks	
Coca-Cola Classic	34.5
Pepsi Cola	38
Dr. Pepper	41

Table 8: Caffeine contents of energy and soft drinks in the United States [158].

the world's most widely consumed psychoactive substance, estimated at 120,000 tonnes per annum [155]. The most widely consumed being coffee, tea, cola nut, cocao pod, guarana are the main source of caffeine and mate as definite previously [156]. The caffeine content in some common sources of caffeine is presented in Table 7 [157].

Table 8 represents the caffeine contents of energy and soft drinks available in the United States [158]. A recent survey has shown that in the United States the average per capita daily intake among adult caffeine consumers is 280 mg [159]. But 30 mg or less of caffeine can alter self-reports of mood and affect behavior and 100 mg per day can lead to physical dependence [160]. In the North America between 80 and 90% of adults and children habitually consume caffeine [161]. Caffeine consumption from soft drinks has dramatically increased over the last few decades, which mostly contain caffeine [162]. Some drink such like root beer, orange soda, cream soda and lemon-lime drinks contain caffeine similar to cola drinks [163]. Coffee ice creams and yogurts deliver a significant dose of caffeine. Chocolate milk, cocoa and milk chocolate candy also contain caffeine; the dose delivered in a usual serving is generally below the danger level [164]. Dark chocolate candy may contain 31 mg of caffeine, which is an exception [165]. Medical products also often contain large amounts of caffeine for example Anacin, Excedrin and Midol deliver 64 to 130 mg per two tablet dose [166].

Regulatory status of caffeine in society and culture

The FDA presently allows only beverages containing not more than 0.02% caffeine in the United States [167]. In contrast, caffeine powder available in the form of dietary supplement is unregulated [168]. The label of prepackaged food must declare the list of ingredients, including food additives like caffeine and this is a regulatory requirement. But there is no rule for mandatory quantitative labeling of caffeine (e.g. mg caffeine per stated serving size) [167,169]. There are a number of food ingredients that naturally contain caffeine. These ingredients must appear in food ingredient lists. In case of food additive caffeine, there is no requirement to identify the amount of caffeine in composite foods containing ingredients that are natural sources of caffeine [167,169]. For less recognized natural sources of caffeine (e.g. guarana, yerba mate) there is no regulatory provision requiring that a food label identify the occurrence of neither caffeine nor state the amount of caffeine existing in the food [169].

Conclusion

It is very difficult to accurately estimate caffeine consumption owing to its numerous distribution, the wide variances in the amount of caffeine delivered in common food as well as large differences in common serving sizes. Caffeine produces significant life-threatening health hazards such as anxiety, insomnia, tachycardia, ectopic beats and reproduction abnormalities even death. The physiological effects of caffeine are almost similar to those produced by other drugs of dependence even though caffeine is not accountable for severe health risks linked with the use of drugs of addiction. Caffeine is a potent drug that complies with the criteria of an addictive substance regarding dependence, tolerance and withdrawal. So care should be taken during ingestion of consumer goods and other caffeinated products since caffeine is a model drug of abuse.

Authors' Contributions

This work was carried out in collaboration between all authors. Author MSU designed the study, wrote the protocol, managed the analyses of the study and prepared the draft of the manuscript. Authors MAS, MFH, MTK and MTI managed the literature searches under supervision of author MSU. Authors MMR and MRR reviewed the scientific contents of the manuscript. All the authors read and approved the final manuscript.

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Competing Interests

The authors proclaim that they have no competing interests.

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